37. (New) The method of Claim 20, wherein the GPCR and the binding partner interact as a result of the ligand binding to the GPCR. --

CA

REMARKS

According to the Official Action, the specification allegedly does not comply with 37 C.F.R. § 1.84(U)(1), since Figures 10B, 11B, 12B and 13B are each presented on multiple panels which are not properly numbered. Accordingly, proposed drawing changes containing the appropriate legends for these figures are submitted herewith. Additionally, the "Brief Description of the Drawings" section of the specification has been amended to correspond to the new figure numbering.

Claims 19 to 23 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Official Action, "[a] critical element of the disclosed invention is the requirement that each member of a pair of interacting proteins be fused to one member of a pair of complementary β-galactosidase mutants."

Claims 19 to 23 were also rejected under 35 U. S. C. §101 because the disclosed invention was allegedly inoperative and lacked utility for the reasons given above.

Claim 19 has been amended to recite a cell that expresses a first protein partner as a fusion protein to one mutant form of reporter enzyme and a second protein partner as a fusion protein to a complementary mutant form of the enzyme. Claim 20 has been amended to recite a plurality of cells that express GPCRs as fusion proteins to one mutant form of reporter enzyme and binding partners as a fusion protein to a complementary mutant form of the enzyme. In view

of the above, it is respectfully submitted that the rejections have been obviated. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 14 was rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 14 has been amended to correct a typographical error. It is respectfully submitted that the amendment to Claim 14 has obviated the rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1 to 18 and 24 to 30 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,342,345 ("Blau") in view of U.S. Patent No. 5,891,646 ("Barak").

Claim 1 recites "[a] method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

a) *providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an interacting protein partner as a fusion protein to another mutant form of enzyme*;

b) exposing the cell to a ligand for said GPCR under said test condition; and

c) *monitoring activation of said GPCR by complementation of said reporter enzyme*;

wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition, and decreased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition.

According to the MPEP, when applying 35 USC 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). MPEP sec. 2141.

It is respectfully submitted that the Official Action has failed to establish a *prima facie* case of obviousness. First, in order to establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Further, the teaching or suggestion to make the claimed combination must be found in the prior art and not in the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

It is respectfully submitted that there is no teaching or suggestion in either Barak or Blau to combine the references in the manner suggested in the Official Action. In particular, Blau broadly discloses methods and compositions for detecting protein-protein interactions using fusion proteins of β-galactosidase mutants. However, G-protein coupled receptors are not specifically disclosed by Blau. Further, while Barak teaches an assay method for GPCRs, the assay method of Barak does not involve the complementation of mutant forms of reporter enzyme

(i.e., neither the GPCR nor the β-arrestin molecule in Barak are expressed as a fusion protein to a mutant form of reporter enzyme). The Official Action has pointed to no teaching or suggestion in either reference to combine the reference teachings in the manner suggested.

Rather, in order to arrive at the Applicant's invention from the teachings of Barak and Blau, the Official Action makes the following assertions:

> An artisan of ordinary skill in the art of molecular biology would have recognized that the method of Barak, et al. was limited by the fact that it did not allow detection of the direct interaction of the fluorescent labeled β-arrestin employed therein with a specific G protein-coupled receptor. (page 6 of the Official Action)
>
> That artisan would have realized that the fluorescent labeled β-arrestin would have accumulated at the cell membrane in response to the activation of any G protein-coupled receptor which might be present in the cell. (page 6 of the Official Action)
>
> . . . that artisan would have appreciated the fact that an accurate measurement of the ligand activation of a particular receptor by employing the method of Barak, et al. would require the inclusion of a control consisting of a cell which is otherwise identical to the test cell except for the absence of the receptor of interest. (pages 6-7 of the Official Action)
>
> That artisan would have understood that the method of detecting protein-protein interaction that was described by Blau, et al. would not have required such a control because it measured the direct interaction of two specific proteins and, therefore, would allow one to measure the direct interaction of β-arrestin with a specific G protein-coupled receptor in an intact cell irrespective of the interaction of β-arrestin with any other G protein coupled receptor which might be present in that cell. (page 7 of the Official Action)
>
> Therefore, that artisan would have found it *prima facie* obvious to have employed the β-galactosidase complementation system of Blau, et al. to detect the interaction of β-arrestin with a particular G protein-coupled receptor to identify agonists and antagonists thereto as taught by Barak, et al. because that artisan would have been more confident that the results obtained by the method of Blau, et al. were representative of the action of the particular receptor of interest. (page 7 of the Official Action)
>
> Further, because it was well known in the art that the activation of G protein-coupled receptors also involved the dimerization of those receptors as well as their interaction with a plurality of cytoplasmic proteins including G protein complexes and G protein-coupled receptor kinases, an artisan would have found it *prima facie* obvious to have employed the β-galactosidase complementation system of

> Blau, et al. to detect the interaction of any of these proteins with one another in an intact cell in response to receptor activation. (page 7 of the Official Action)

It is respectfully submitted that the above line of reasoning could only have been arrived at with the benefit of the Applicant's disclosure. For example, the Official Action makes reference to what one of ordinary skill in the art would have "recognized", "realized", "appreciated" or "understood" without providing support for these statements. In fact, the alleged shortcomings of the Barak assay method referred to in the Official Action are only apparent given the Applicant's disclosure of an improved receptor function assay for G-protein coupled receptors. As set forth in The MPEP:

> . . . the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination . . . The tendency to resort to "hindsight" based upon Applicant"s disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. MPEP sec. 2142.

Since the rejection is an impermissible hindsight reconstruction of the Applicant's invention, reconsideration and withdrawal of the rejection is respectfully requested.

Additionally, the statement in the Official Action of what was allegedly "well known in the art" is unsupported by any evidence of record. Accordingly, it is respectfully requested that evidence in support of the aforementioned statement be provided.

Further, the Official Action has also failed to establish that one of ordinary skill in the art could have made the proposed combination or modification with a reasonable expectation of success. It is well established that references can be modified or combined to reject claims as *prima facie* obvious only if there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, at least some degree of predictability is

required to show reasonable expectation of success. See MPEP §2143.02. Additionally, the reasonable expectation of success must be found in the prior art and not in the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP sec. 2143.

The Official Action has pointed to no teaching in the references of record that would establish that the proposed combination could have been made with a reasonable expectation of success. It is respectfully submitted that such evidence is not present in either reference. As set forth above, G-protein coupled receptors are not disclosed by Blau. Further, while Barak teaches an assay method for GPCRs, the assay method of Barak does not involve the complementation of mutant forms of reporter enzyme (i.e., neither the GPCR nor the β-arrestin molecule in Barak are expressed as a fusion protein to a mutant form of reporter enzyme). Since neither reference adequately establishes that the complementation of mutant forms of reporter enzyme can be adapted for use with G-protein coupled receptors with a reasonable expectation of success, it is respectfully submitted that the claims are patentable over the cited references. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Additionally, the modification of the Barak reference in the manner set forth in the Official Action would fail to establish a case of *prima facie* obviousness since the modification would involve a change in the principle of operation of the reference. It is well established that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). In Ratti, the court reversed an obviousness rejection holding that the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.). See MPEP 2143.01.

Similarly, the modification proposed in the Official Action would require a substantial reconstruction and redesign of the assay method of Barak. Namely, in the assay methods of Barak, the test cell expresses GPCR and a conjugate of β-Arrestin and a visually detectable molecule. According to Barak, the test cell is then observed for evidence of translocation of the detectable molecule (see, for example, column 2, lines 35-37 of Barak). For example, the translocation of the visually detectable molecule (e.g., from the cytosol to the cell edge) can be used to assay G-protein coupled receptor activity (see, for example, column 2, lines 43-52 of Barak). Thus, in Barak the movement of a visually detectable molecule bound to the β-arrestin molecule is being monitored. The principle of operation of Barak is therefore radically different than that set forth in Claim 1 wherein *the complementation of mutant forms of a reporter enzyme*, one expressed as a fusion protein to a GPCR and another as a fusion protein to an interacting protein partner, is being monitored. Accordingly, it is respectfully submitted that the invention as set forth in Claim 1 is patentable over the cited references. In view of the above, reconsideration and withdrawal of the rejection of Claim 1 is therefore respectfully requested.

Claims 2-8 depend either directly or indirectly from Claim 1 and are therefore also patentable over the cited references for at least the reasons set forth above with respect to Claim1. Reconsideration and withdrawal of the rejections of these claims is therefore also respectfully requested.

Claim 9 recites "[a] method for screening a β-arrestin protein or an unidentified arrestin or arrestin-like protein or fragment and mutant form thereof for the ability to bind to activated GPCRs, comprising:

~~a) *providing a cell that:*~~

i) expresses at least one GPCR as a fusion protein to a reporter enzyme; and

ii) contains a conjugate comprising a test β-arrestin protein as a fusion protein with another reporter enzyme;

b) exposing the cell to a ligand for said at least one GPCR; and

c) detecting enzymatic activity of the complemented reporter enzyme;

wherein an increase in enzymatic activity in the cell indicates β-arrestin protein binding to the activated GPCR."

Claim 10 recites "[a] method for screening a test compound for G-protein-coupled receptor (GPCR) agonist activity, comprising:

a) *providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme*;

b) exposing the cell to a test compound; and

c) detecting complementation of said reporter enzyme;

wherein increased reporter enzyme activity after exposure of the cell to the test compound indicates GPCR agonist activity of the test compound."

Claim 18 recites "[a] method of screening a test compound for G-protein-coupled receptor (GPCR) antagonist activity, comprising:

a) *providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme*;

b) exposing the cell to said test compound;

c) exposing the cell to an agonist for said GPCR; and

d) detecting complementation of said reporter enzyme;

~~where exposure to the agonist occurs at the same time as, or subsequent to, exposure to~~ the test compound, and wherein decreased reporter enzyme activity after exposure of the cell to the test compound indicates that the test compound is an antagonist for said GPCR."

Claim 24 recites "[a] substrate having deposited thereon a plurality of cells, *said cells expressing at least one GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme*."

As set forth above, Blau taken with Barak fail to teach or reasonably suggest assaying GPCR activity by monitoring complementation of mutant forms of a reporter enzyme. Claims 9, 10, 18 and 24, which recite a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme, are therefore patentable over the cited references for at least the reasons set forth above with respect to Claim 1. Claims 11-17 and 25-26 depend from Claims 10 and 24, respectively, and are therefore also patentable over the references of record. Reconsideration and withdrawal of the rejections of these claims is therefore respectfully requested.

Claim 19 recites "[a] method of screening a cell for the presence of a G-protein-coupled receptor (GPCR) responsive to a GPCR ligand, comprising:

a) *providing a cell that expresses a first protein partner as a fusion protein to one mutant form of reporter enzyme and a second protein partner as a fusion protein to a complementary mutant form of the enzyme, wherein the first and second protein partners interact downstream in the GPCR pathway*;

b) exposing the cell to a GPCR ligand; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase or decrease in enzymatic activity after exposure of the cell to the GPCR agonist indicates that the cell contains a GPCR responsive to said ligand."

~~Claim 20 recites "[a] method of screening a plurality of cells for those cells which contain~~ a G- protein-coupled receptor (GPCR) responsive to a GPCR ligand, the method comprising:

a) *providing a plurality of cells that express the GPCR as a fusion protein to a first*

mutant form of reporter enzyme and a binding partner of the GPCR as a fusion protein to a second mutant form of the enzyme complementary to the first mutant form of the enzyme;

b) exposing the cells to a GPCR ligand; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase or decrease in enzymatic activity after exposure of the cell to the GPCR ligand indicates that the cell contains a GPCR responsive to the ligand."

Claim 27 recites "[a] method of detecting G-protein-coupled receptor (GPCR) pathway activity in *a cell expressing at least one GPCR and containing a first protein partner as a fusion protein to one mutant form of reporter enzyme and a second protein partner as a fusion protein to a complementary mutant form of the enzyme*, wherein the first and second protein partners interact downstream in the GPCR pathway and wherein activity of said enzyme indicates activation of the GPCR pathway."

As set forth above, Blau taken with Barak fail to teach or reasonably suggest monitoring GPCR activity by complementation of mutant forms of a reporter enzyme. Therefore, methods as set forth in Claims 19, 20 or 27 comprising monitoring the interaction of a GPCR and a binding partner or monitoring the interaction of first and second protein partners downstream in a GPCR pathway would also be patentable over the cited references. Claims 19, 20, and 27, as well as Claims 21- 23 and 31-34 (which depend from Claim 20) and Claims 28-30 (which depend from Claim 27), are therefore patentable over Blau, et al. taken with Barak, et al. Reconsideration and withdrawal of the rejections of these claims is therefore respectfully requested.

Claims 16 and 36 can be further distinguished from the references of record. Claims 16 and 36 depend from Claim 10 and recite that the cell endogenously expresses one or more G-protein-coupled receptors. There is no teaching or suggestion in the references of record of a method of monitoring GPCR activity as claimed wherein the cell endogenously expresses a

GPCR. Endogenous GPCR expression does not interfere with the claimed assay. Thus, GPCR activity can be monitored (i.e., specific detection of protein-protein interactions can be achieved) using the claimed method regardless of whether or not the cell endogenously expresses a GPCR. In view of the above, it is respectfully submitted that Claims 16 and 36 are patentable over the references of record.

Claims 31 - 35 have been added to further define the invention. Claims 31 and 32 depend from Claim 20 and further recite that the enzyme activity is detected either in a mixture of the plurality of cells (Claim 31) or by isolating clones of individual cells and detecting enzyme activity in the clones of individual cells (Claim 32). Claims 33 and 34 depend from Claim 20 and further recite that the binding partner is either "a cellular component that directly or indirectly modulates GPCR activation or inactivation" (Claim 33) or an arrestin (Claim 34). Claim 35 also depends from Claim 20 and recites that the plurality of cells express multiple GPCRs as a fusion protein to the first mutant form of reporter enzyme. Each of these claims is patentable over the references of record for at least the reasons set forth above for Claim 20. In addition, Claims 32 - 35 can be further distinguished from the references of record. In particular, there is no teaching or suggestion in the references of record of a method as set forth in Claim 32 wherein enzyme activity is detected by isolating clones of individual cells and detecting enzyme activity in the clones of individual cells. Further, there is no teaching or suggestion in the references of record of a method as set forth in Claims 33 or 34, wherein interactions between a GPCR and "a cellular component that directly or indirectly modulates GPCR activation or inactivation" or between a GPCR and arrestin are monitored. Finally, there is no teaching or suggestion in the references of

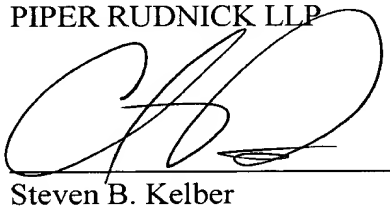
record of a method as set forth in Claim 35 wherein cells express multiple GPCRs as a fusion protein to the first mutant form of reporter enzyme. In view of the above, it is respectfully submitted that Claims 31 - 35 are also patentable over the references of record.

CONCLUSION

All rejections having been addressed by the present amendments and response, Applicants believe that the present case is in condition for allowance and respectfully request early notice to that effect. If any issues remain to be addressed in this matter which might be resolved by discussion, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

PIPER RUDNICK LLP



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SERIAL NO. 09/654,499

DOCKET NO.: 4085-226-27

MARKED-UP COPY OF PARAGRAPHS, AS AMENDED

Replacement for second full paragraph at page 12, lines 9 and blank line immediately thereafter:

[FIGURE 10B.] FIGURES 10B-10J. Nucleotide [and amino acid sequences (SEQ ID NOS: 1 and 2)] sequence for [PICAST] pICAST ALC.

Replacement for fourth full paragraph at page 12, line 16:

[FIGURE 11B.] FIGURES 11B-11J. Nucleotide sequence [(SEQ ID NO: 3)] for pICAST ALN.

Replacement for first full paragraph at page 13, line 1:

[FIGURE 12B.] FIGURES 12B-12J. Nucleotide sequence [(SEQ ID NO: 4)] for pICAST OMC.

Replacement for third full paragraph at page 13, line 8:

[FIGURE 13B.] FIGURES 13B-13J. Nucleotide sequence [(SEQ ID NO: 5)] for pICAST OMN.

SERIAL NO. 09/654,499

DOCKET NO.: 4085-226-27

MARKED-UP COPY OF AMENDED CLAIMS

14. (Twice Amended) A method according to Claim 10, wherein the cell expresses a [GPCR, a] β-adrenergic receptor.

19. (Amended) A method of screening a cell for the presence of a G-protein-coupled receptor (GPCR) responsive to a GPCR [agonist] ligand, comprising:

a) providing a cell[, said cell containing a conjugate comprising a β-arrestin protein as a fusion protein with a reporter enzyme] that expresses a first protein partner as a fusion protein to one mutant form of reporter enzyme and a second protein partner as a fusion protein to a complementary mutant form of the enzyme, wherein the first and second protein partners interact downstream in the GPCR pathway;

b) exposing the cell to a GPCR [agonist] ligand; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase or decrease in enzymatic activity after exposure of the cell to the GPCR [agonist] ligand indicates that the cell contains a GPCR responsive to said [agonist] ligand.

20. (Twice Amended) A method of screening a plurality of cells for those cells which contain a G-protein-coupled receptor (GPCR) responsive to a GPCR [agonist] ligand, the method comprising:

~~a) providing a plurality of cells[, said cells containing a conjugate comprising a~~ β-arrestin protein as a fusion protein with a reporter enzyme] that express the GPCR as a fusion protein to a first mutant form of reporter enzyme and a binding partner of the GPCR as a fusion

protein to a second mutant form of the enzyme complementary to the first mutant form of the enzyme;

b) exposing the cells to a GPCR [agonist] ligand; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase or decrease in enzymatic activity after exposure of the cell to the GPCR [agonist] ligand indicates [β-arrestin protein binding to a GPCR, thereby indicating] that the cell contains a GPCR responsive to [said GPCR agonist] the ligand.

27. (Amended) A method of detecting G-protein-coupled receptor (GPCR) pathway activity in a cell expressing at least one GPCR and containing a first protein partner as a fusion protein to one mutant form of reporter enzyme and a second protein partner as a fusion protein to a complementary mutant form of the enzyme, wherein the first and second protein partners interact downstream in the GPCR pathway and [β-arrestin protein as a fusion protein with a reporter enzyme;] wherein activity of said [enzymatic activity] enzyme indicates activation of the GPCR pathway.

In re RATTI, 123 USPQ 349 (CCPA 1959)

In re RATTI

(CCPA)
123 USPQ 349

Decided Sept. 30, 1959
Appl. No. 6452
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Evidence—Judicial notice (§ 36.20)

It is common knowledge that resilient deformable materials such as natural or synthetic rubber are incompressible, i.e., while they may be deformed, this can occur only if design and mounting of part permits resilient material to change its shape in response to applied forces.

2. Patentability — Anticipation — Combining references (§ 51.205)

Patentability — Anticipation — Modifying references (§ 51.217)

Combination of J patent with C patent is not proper ground for rejection of claims since combination would require substantial reconstruction and redesign of elements shown in C as well as change in basic principles under which C construction was designed to operate; once applicant taught how this could be done, redesign may, by hindsight, seem to be obvious to one having ordinary skills in art, but, when viewed as of time applicant's invention was made, and without benefit of applicant's disclosure, court finds nothing in art of record which suggests applicant's novel device.

3. Court of Customs and Patent Appeals—Issues determined—Ex parte patent cases (§ 28.203)

~~Rejection reversed by Board is not before court.~~

4. Patentability—In general (§ 51.01)

Novelty alone is not enough for patentability.

5. Patent grant—In general (§ 50.01)

Applicant is entitled to patent, under the statutes, unless one of the prohibitory provisions of statutes applies.

6. Patentability—In general (§ 51.01)

Patentability—Evidence of—In general (§ 51.451)

Patentability—Utility (§ 51.75)

Statutory requirements for patentability are novelty, usefulness, and unobviousness, as provided in 35 U.S.C. 101, 102, and 103; while proof that invention is better or possesses advantages may be persuasive of existence of any one or all of the requirements, and hence be indicative of patentability, Congress has not made such proof a prerequisite to patentability; moreover, Congress has never required that each and every patentable invention involve "progress" in the sense that it must possess some definite advantage over prior art; hence, it is improper to reject claim on ground that it does not possess some definite advantage over prior art; whileR.S. 4893 may be said to have given Commissioner some discretion in refusing to grant patent on an otherwise patentable invention unless "the same is sufficiently useful and important," Congress removed this provision from new 35 U.S.C. 131; this is further indication that it is intent of Congress that patentability be determined solely by sections 101, 102, and 103.

7. Court of Customs and Patent Appeals—In general (§ 28.01)

Pleading and practice in Patent Office—In general (§ 54.1)

It is duty of Patent Office and Court of Customs and Patent Appeals to apply law as Congress wrote it.

Particular patents—Oil Seal

Ratti, Oil Seal, claims 1, 4, 7, and 10 of application allowed.

Case History and Disposition:

Appeal from Board of Appeals of the Patent Office.

Application for patent of Ferdinand J. Ratti, Serial No. 359,325, filed June 3, 1953; Patent Office Division 52. From decision rejecting claims 1, 4, 7, and 10, applicant appeals. Reversed; Kirkpatrick, Judge, dissenting with opinion in which Worley, Chief Judge, joins.

Attorneys:
CROMWELL, GREIST & WARDEN (RAYMOND L. GREIST of counsel) both of Chicago, Ill.,

for appellant.

CLARENCE W. MOORE (S. WM. COCHRAN of counsel) for Commissioner of Patents.

Judge:
Before WORLEY, Chief Judge, RICH, MARTIN, and SMITH, Associate Judges, and KIRKPATRICK, Judge *.

Opinion Text

Opinion By:
SMITH, Judge.

This is an appeal from the decision of the Board of Appeals of the United States Patent Office affirming the rejection by the Primary Examiner of claims 1, 4, 7 and 10 of appellant's application serial No. 359,325, filed June 3, 1953, for a patent on an "Oil Seal" for sealing the space between a bore in a housing and a relatively movable shaft centrally located in the bore.

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Claim 1 is representative of claims 4 and 7 and reads:

> 1. A seal for insertion in a cylindrical bore in a housing about a relatively movable centrally located shaft, comprising an annular bore-engaging mounting portion of resiliently deformable material for endwise insertion in and statically sealed engagement with the bore in the housing, an annular shaft-engaging portion connected with said bore-engaging portion for running engagement with the shaft, and a *metal ring* located adjacent one end of said bore-engaging portion, said ring being *provided with a plurality of axially extending outwardly biased spring fingers in outwardly clamped engagement with said bore-engaging portion* inwardly of the outer periphery of the latter, and said ring being *also provided* outwardly of said bore-engaging portion *with means for detachably connecting the ring to the housing* outwardly of the bore in the latter. (Emphasis ours.)

Claim 10 differs from the other claims on appeal and reads:

> 10. A seal for insertion in a cylindrical bore in a housing about a relatively movable centrally located shaft, comprising a sealing ring having an outer bore-engaging portion of resiliently deformable material, which portion is of somewhat larger diameter than the bore in the housing, for press-fit insertion in the bore, and a *metal retaining ring* associated with the sealing ring, said retaining ring being connected with the sealing ring and being provided outwardly of the latter *with resiliently yieldable hook formations which are adapted to be sprung into interlocking engagement with a complementary formation associated with the housing outwardly* of the bore, which engagement acts to prevent axial displacement of the sealing ring relative to the bore in the housing. (Emphasis ours.)

The references in the case are:

> Roth, 1,546,942, July 21, 1925.
>
> Norton, 1,951,034, Mar. 1, 1934.
>
> Jepson, 2,544,324, Mar. 6, 1951.
>
> Chinnery et al. (British), 578,526, July 2, 1946.

Appellant's shaft seal comprises an annular sealing member of resilient deformable material which is adapted to be inserted into a cylindrical bore surrounding a relatively movable shaft. The inner portion of the sealing member is provided with a flexible lip which is held in engagement with the shaft by a garter spring. In the outer portion of the sealing member, an annular slot is provided which is concentric with and spaced from the outer periphery of the sealing member. This slot extends axially from the end of the member and provides a pocket in which the axially extending outwardly biased spring fingers of a metallic attaching ring are located. This construction permits the spring fingers to exert a force on the resilient material in the direction of the annular wall of the bore to provide and maintain a snug engagement between the outer surface of the resilient member and the inner surface of the bore. The metallic attaching ring is also provided with radially extending resilient hooks located outwardly of the bore engaging portion of the resilient member. The housing is provided with a complementary formation outwardly of the bore which is engaged by the resilient hooks to provide a snap-on connection between the bore and the seal.

The Roth and Norton patents were relied upon by the examiner in rejecting claim 10, and since both references were considered by the board, we have included them in our consideration of this case. Roth shows a gasket structure for steam train line hose couplings. Norton shows an adjustable repair clamp for bell and spigot joints in which there is provided a sheet metal bridge piece "preferably of spring material." The bridge piece is sprung into interlocking engagement with a structural portion of the clamp and exerts its force on a resilient packing ring which, if desired, may be cemented to it.

The Chinnery et al. patent is the reference principally relied upon by the Patent Office. It shows a housing provided with a bore surrounding a centrally located shaft. A reinforced and "stiffened" sealing member formed of a material such as rubber, is press fitted into the space between the bore and the shaft. The sealing member has an inner lip held in contact with the shaft by a garter spring. The bore engaging portion of the sealing member is "stiffened" by an axially extending cylindrical sheet metal casing which acts as a reinforcing member for a definite purpose which is described by Chinnery et al. as follows:

> Owing to the limited radial space within which the oil seal is to be accommodated, the holding portion of the oil seal cannot be stiffened by being massive. Consequently the holding portion of the present oil seal is stiffened in the known manner by a reinforcement, which may either encase or line, or alternatively constitute, such holding portion and therefore makes the press-fitting contact with the machine part stationary relatively thereto, *or may be an internal reinforcement in the sense that it does not make press-*
>
> Page 351
>
> fitting contact with the machine part stationary relatively thereto. (Emphasis ours.)

In Fig. 8 Chinnery et al. shows a radially extending flange at the outer edge of a reinforcing member of the internal reinforcement type which flange extends beyond the sealing member "to such an extent as to serve as a means of attachment of the oil seal to the housing *i,* additional to the interference press fit of the holding portion *a* in the housing recess *g.* " The aforesaid flange is shown attached to the housing by screws or bolts.

The Jepson patent relates to a gasket for sealing the space between the upper and lower vessels of a vacuum-type coffee maker. The gasket is an annular rubber member attached to the lower part of the upper vessel and is designed to fit into the upper part of the lower one. Located in a groove in the gasket is a sleeve member provided with axially and downwardly extending spring fingers which are so biased radially as to urge the lower peripheral portion of the gasket outwardly, thus effecting a tight engagement with the mouth of the lower vessel.

Claims 1, 4, and 7 stand rejected on Chinnery et al. in view of Jepson, on the ground that it would not require "invention" to replace the cylindrical sheet metal reinforcing member, which is secured to

the Chinnery et al. sealing member, by an annular set of outwardly biased spring fingers shown by Jepson.

The problems which were solved by appellant's invention existed in this art at the time of his invention despite the Chinnery et al. disclosures. It was appellant rather than Chinnery et al. who provided the art with a shaft seal in which the resilient element of the seal could be readily inserted into a bore in the housing so that it could be removed from the bore and replaced by a new sealing element without mutilation of the sealing surface of the bore. This is particularly important, the specification points out, where the bore is formed in light metal alloys such as are used in aircraft engines and which are relatively soft and easily damaged. In appellant's oil seal, the resilient seal is so constructed that when mounted in the bore, it will establish and maintain a fluid tight relationship between the outer peripheral surface of the resilient seal member and the inside of the bore. Where either natural or synthetic rubber is used as the resilient sealing member in such seals, the rubber in time will take a set or lose its resiliency at least to the extent that the seals soon become ineffective to prevent leakage of oil. When subjected to mechanical pressures and heat, such a rubber sealing element loses its sealing effectiveness at an accelerated rate. The problems in the oil sealing art arising from such use of resilient sealing elements appear to have persisted because of the failure of the art to recognize these characteristics of the rubber sealing element and to so design the resilient element and the mounting therefor as to assure holding the outer circumference of the resilient sealing element in static oil-sealing contact with the inner circumference of the bore in which it is inserted.

Appellant's seal differs from the art of record in at least three respects:

> (1) The provision of the annular slot which extends axially inward from one end of the resilient sealing element. This feature is claimed as part of the combination set forth in claim 4.
>
> (2) The outwardly biased resilient spring means or fingers inserted in the resilient sealing element. These means are claimed as part of the combination of claims 1, 4 and 7.
>
> (3) The "snap-on" connector which holds the resilient sealing element and engages with a complementary formation associated with the housing outwardly of the bore. This feature is in the combination of claim 10.

The patents cited by the examiner, either alone or in combination, do not disclose a resilient shaft sealing element having these features.

[1] It is common knowledge that resilient deformable materials such as either natural or synthetic rubber are incompressible, that is, while they may be deformed, this can occur only if the design and mounting of the part permits the resilient material to change its shape in response to the applied forces.

The seal construction disclosed in Chinnery et al. is such that the "interference press fit" which that patent calls for is alone relied on to keep the seal tight. There is nothing in the Chinnery et al. patent to show how the resilient sealing element is *maintained* in resilient contact with the bore otherwise than by the resiliency of the rubber. If and when that resiliency is lost, the sealing effect will be impaired.

Considering the incompressible nature of the rubber in the sealing element disclosed in Chinnery et al., its stiffening and reinforcement by the cylindrical sheet metal member, and its "interference press fit" in the bore, it seems clear to us that the Chinnery et al. seal cannot function in the manner of appellant's seal. Now, as to the contention that Jepson would suggest inserting a set of spring fingers, the resilient element of Chinnery et al. is forced so tightly into the bore

and is so "stiffened" that the use of the resilient spring fingers of Jepson could not possibly increase the resilient deformation of the Chinnery et al. seal in the direction of the bore or increase the sealing engagement of the seal with the bore. The teaching of the Chinnery et al. patent points away from the addition of any spring element. On the other hand, we find nothing in the disclosure of Jepson's coffee maker gasket to suggest that any part of it has applicability to shaft seals. The two arts are at least somewhat remote from each other even if they both involve sealing.

[2] We, therefore, find that Chinnery et al. did not teach the shaft sealing art how to solve the problems which existed in that art at the time of appellant's invention. We hold, further, that the combination of Jepson with Chinnery et al. is not a proper ground for rejection of the claims here on appeal. This suggested combination of references would require a substantial reconstruction and redesign of the elements shown in Chinnery et al. as well as a change in the basic principles under which the Chinnery et al. construction was designed to operate.

Once appellant had taught how this could be done, the redesign may, by hindsight, seem to be obvious to one having ordinary skills in the shaft sealing art. However, when viewed as of the time appellant's invention was made, and without the benefit of appellant's disclosure, we find nothing in the art of record which suggests appellant's novel oil seal as defined in claims 1, 4 and 7.

We shall now consider the rejection of claim 10, remarking first that it differs from claims 1, 4 and 7 in that it is directed to a combination of a housing bore, a resilient sealing ring and a metal retaining ring connected to the sealing ring, wherein the metal ring has *resilient hooks* which secure the seal in the bore. This claim is not limited to the outwardly biased spring fingers.

The examiner rejected claim 10 on two grounds: (1) that substitution for the screw securing means of Chinnery et al. of a series of spring hooks such as disclosed by Norton would not involve patentable invention, and (2) unpatentability over Roth.

[3] We shall first dispose of the second rejection. The board held that claim 10 is drawn to a combination of a sealing ring and a housing bore in which the sealing ring is detachably placed and that Roth discloses nothing of this nature. The board therefore reversed the rejection on Roth and consequently it is not before us.

As to the first rejection, the board recognized that it was on the ground of unpatentability "over Chinnery et al. in view of Norton" and pointed out that the examiner could see nothing patentable in substituting spring hook attaching means shown in Norton for the screws of Chinnery et al. It then said:

> Appellant argues that the references fail to suggest or teach how the proposed [claimed] combination could be made and after a careful consideration of the references, *we have concluded that he is correct in this respect. We therefore concede that the claim * * * defines novelty over the disclosure of Fig. 8 of Chinnery et al.* Novelty alone however, is no proper basis for the allowance of a claim. (Emphasis ours.)

[4] Although, in reaching this conclusion, the board made no reference to Norton, the context compels the conclusion that novelty was found notwithstanding the disclosure of Norton, taken together with Chinnery et al. We fully agree, of course, with the board's statement that novelty alone is not enough for patentability.

With the next statement of the board, in explanation of its affirmance of the rejection of claim 10, we do not agree. It reads:

> In order to *properly* define invention [meaning, of course, *patentable* invention], a claim should clearly define a structure *which possesses some definite advantage over the prior art.* As far as we can determine there is *no better* combination of housing and seal produced by

> using a series of snap fastener connections to connect the seal to the housing, as in appellant's structure, over using a series of bolts, as in the structure shown by Chinnery et al. Both act to merely detachably connect one element to another element and as far as we can find are merely equivalent connecting means especially in the absence of any unexpected result *or advantage* being obtained, by using one means in preference to the other, on which the record before us is entirely silent. (Emphasis ours.)

If we may extract from the foregoing what we understand to be the essence of the board's position in the matter, it is that claim 10 is not patentable, though it defines a combination which is novel over the disclosures of the references, because the claimed combination has not been shown to be any better than, or to possess any advantage over, what was known to the art.

[5][6] As was pointed out in In re Stempel, Jr., 44 CCPA 820, 241 F.2d 755, 113 USPQ 77, an applicant is entitled to a patent, under the statutes, unless one of the prohibitory provisions of the statutes applies. The statutory requirements

for patentability, broadly stated, are novelty, usefulness and unobviousness, as provided in 35 U.S.C. sections 101, 102, and 103. While it is true that proof that an invention *is* better or *does* possess advantages may be persuasive of the existence of any one or all of the foregoing three requirements, and hence be indicative of patentability, Congress has not seen fit to make such proof a prerequisite to patentability. [1]

[7]Appellant's invention, as defined in claim 10, has been held by the board to possess novelty over the disclosure of Chinnery et al. Just what the board thought about the pertinency of Norton is obscure but it seems to have regarded this reference as of little moment. Appellent in his brief here said that Norton was held by the board to have no bearing on the invention and the Patent Office brief said that the appellant was correct in so stating and that the court need not consider it. We are, therefore, virtually without any reference against claim 10 except Chinnery et al. and the rejection thereon is predicated solely on a theory of patentability we find to be outside of the patent statutes, namely, that the combination of claim 10 is, by reason of the use of spring retaining hooks instead of a series of bolts, *no better* than the combination of Chinnery et al. However intriguing such a ground of rejection may be, it is the duty of the tribunals of the Patent Office and of this court to apply the law as Congress has written it. While the provisions of the formerR.S. 4893 may be said to have given the Commissioner some discretion in refusing to grant a patent on an otherwise patentable invention unless "the same is sufficiently useful and important," when the Patent Codification Act of 1952 was enacted, Congress removed this provision from old section 36 of title 35, now section 131. We take this as a further indication that it is the intent of Congress that patentability be determined solely by the provisions of sections 101, 102 and 103. We therefore reverse the board on this ground of rejection of claim 10.

If the issue before us were whether or not the spring hooks *are* better than the Chinnery et al. bolts—and we consider this in the event we have misapprehended the position of the board—we would hold that they are, on the basis of what is disclosed in the application. This retaining means seems to possess many advantages over screws. Similarly, if the board was intending to say that the hooks and the bolts are merely equivalent connecting means and that claim 10 is unpatentable because its combination differs from the prior art only in the substitution of an equivalent for one element in an old combination, then we would also have to disagree since we think it is clear that the use of the spring hooks produces a result quite different from the bolts of Chinnery et al. On the record before us no reference relied on shows any spring hooks nor does it contain any support for the contention that bolts and spring hooks are equivalents.

For the foregoing reasons we reverse the rejection of claim 10.

The rejections of claims 1, 4, 7 and 10 are *reversed.*

Footnotes

Footnote 1. A critical essay on the existing law has recently appeared under the title "A Proposal for: A Standard of Patentability; Consonant Statutory Changes; A Manual on Determination of Patentability," by Malcolm F. Bailey, 41 J.P.O.S. 192-225, 231-257. It advocates, as we understand it, that the present law should be changed to set up as the test for patentability, in place of the requirement of section 103 that an invention be unobvious, a requirement that the invention involve *progress,* which the author finds in the constitutional provisions. Congress has not seen fit to include in the statutes, at any time during the past 169 years so far as we are aware, a requirement that each and every patentable *invention* shall involve "progress" in this sense, i.e., that each new invention must also be shown to possess some definite advantage over the prior art. The author relates the term "progress" to individual inventions and then gives it the connotation that each such invention should be a technical advance, improvement or betterment. The very making of the suggestion to change the law is an indication that the existing law is otherwise.

Concurring Opinion Text

Concur By:
MARTIN, Judge, concurs in result.

Dissenting Opinion Text

Dissent By:
KIRKPATRICK, Judge, dissenting, in which WORLEY, Chief Judge, joins.

I think that the board's rejection of claims 1, 4 and 7 should be affirmed. The central idea and the most important feature of these three claims, as well as of allowed claim 5, is the exertion of outwardly directed pressure upon the bore engaging portion of the sealing member, the result accomplished being to counteract the tendency of rubber to "set" or lose its resiliency and so become ineffective to prevent leakage. Jepson comes very close to completely anticipating this feature of the patent. All that would be necessary to make the anticipation complete would be to provide the Jepson seal with a shaft engaging portion and, incidentally, claim 7 does not specify any shaft engaging portion.

Of course, it was necessary that the seal be attached to the bore in a manner to prevent its displacement. Chinnery provides a flange and screws for this purpose and none of the three claims referred to calls for anything more specific than "means." Thus it seems clear that

claims 1, 4 and 7 show no patentable novelty as against the prior art of Chinnery plus Jepson.

The only question is whether Jepson is in a nonanalogous art sufficiently remote from that of the application to put it beyond the probability that it would be considered by persons skilled in the art endeavoring to solve the problem to the solution of which the application is directed. I do not think that it is. Jepson was trying to meet exactly the same problem as the application under consideration, namely, to provide a compressible seal which could be readily detached or inserted in a cylindrical bore but which would maintain a firm and leakproof seat on the bore when in place. I agree with the Solicitor's argument that one seeking to improve a machinery seal would reasonably be expected to investigate not only machinery seals but seals in other arts where similar problems would be encountered. See In re O'Connor, 34 CCPA 1055, 161 F.2d 221, 73 USPQ 433 .

Claim 10 stands on a somewhat different basis. This claim entirely omits what I think, and have stated above, to be the heart of the application. In substance, claim 10 really amounts to no more than a claim for a hook formation to interlock with the housing of a bore in order to hold a press fit seal in place. [1] Chinnery discloses means to serve the same purpose consisting of screws.

The board conceded that the combination disclosed in claim 10, consisting of spring hooks to fasten a press fit seal to the bore, disclosed novelty over Chinnery but not patentable novelty.

I do not read the opinion of the board as predicating its conclusion of want of invention on the theory that in order to be patentable a combination must have some distinct advantage over the prior art. The board stated that there was nothing in the record to show that the substitution of hooks for screws produced any unexpected result or advantage and, therefore, concluded that the introduction of hooks did not create patentable novelty, but was a mere substitution of equivalents. The statement that the spring hooks of Ratti were no better than the screws of Chinnery was directed toward this point and seemingly was added to fortify the board's finding of equivalency rather than to propound a theory of patentability. I agree with the board that this claim, though it may show novelty over Chinnery, does not show patentable novelty, and I would affirm its rejection.

Footnotes

Footnote 1. Chinnery discloses a press fit seal, but no one has suggested that there is anything new about such a device and the specification of the application before us concedes that it is old in the art.

Footnote * United States Senior District Judge for the Eastern District of Pennsylvania, designated to participate in place of Judge O'CONNELL, pursuant to the provisions of Title 28, United States Code, Section 294(d).

- End of Case -

Print-Friendly Version

In re Merck & Co., Inc., 231 USPQ 375 (CA FC 1986)

In re Merck & Co., Inc.

(CA FC)
231 USPQ 375

Decided September 8, 1986
No. 85-2740
U.S. Court of Appeals Federal Circuit

Headnotes

PATENTS

1. Patentability -- Invention -- Specific cases -- Chemical (§ 51.5093)

Board of Patent Appeals and Interferences' decision sustaining rejection for obviousness of reexamination claims for antidepressant drug amitriptyline was proper, since claimed drug is structurally similar to other prior art psychotropic compound, imipramine, which is known to possess antidepressive properties, and thus one skilled in medicinal chemical arts would have expected amitriptyline to resemble imipramine in alleviation of depression in humans.

Case History and Disposition:

Appeal from Patent and Trademark Office Board of Patent Appeals and Interferences.

Reexamination request, Control No. 90/000264, to reexamine patent of Edward L. Englehardt, Patent No. 3,428,735, issued February 18, 1969, on application, Serial No. 662,907, filed August 24, 1967, as continuation-in-part of application Serial No. 855,981, filed November 30, 1959. From decision sustaining decision rejecting claims 1-3 in reexamination application, applicant appeals. Affirmed; Baldwin, Circuit Judge, dissenting with opinion.

Attorneys:

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Richard E. Schafer, Associate Solicitor (Joseph F. Nakamura, Solicitor, and Fred E. McKelvey, Deputy Solicitor, on the brief) for Patent and Trademark Office.

DonaldR. Dunner, and Finnegan, Henderson, Farabow, Garrett & Dunner, both of Washington, D.C. (Robert D. Bajefsky, Carol P. Einaudi, and Finnegan, Henderson, Farabow, Garrett & Dunner, all of Washington, D.C., on the brief, and Beryl L. Snyder, Elmwood Park, N.J., of counsel) for intervenor Biocraft Laboratories, Inc.

Judge:
Before Davis, Baldwin, and Archer, Circuit Judges.

Opinion Text

Opinion By:
Davis, Circuit Judge.

This is an appeal from a final decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), sustaining the rejection of claims 1 through 3 in the reexamination application [1] of U.S. Patent No. 3,428,735 [2] (the '735 patent) as unpatentable under 35 U.S.C. § 103. We affirm.

I. BACKGROUND

A. *The Invention*

The invention is directed to a method of treating human mental disorders; the method involves treating depression in humans by the oral administration of 5-(3-dimethylaminopropylidene) dibenzo [a,d] [1,4] cycloheptadiene (commonly known as and hereafter referred to as "amitriptyline"), or the hydrochloride or hydrobromide salts thereof,

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in a particular dosage range. Amitriptyline has the following chemical structure:
Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

As representative of the invention, claim 1 reads:

> 1. A method of treating human mental disorders involving depression which comprises orally administering to a human affected by depression 5-(3-dimethylaminopropylidene) dibenzo [a,d] [1,4] cycloheptadiene or its non-toxic salts in daily dosage of 25 to 250 mg. of said compound.

Remaining claims 2 and 3 are dependent from claim 1 and add limitations pertaining to the use of the hydrochloride and hydrobromide salts of amitriptyline, respectively.

B. *Related Proceedings*

On March 10, 1977 an application, Serial No. 776,464 (the '464 application), was filed for reissue of the '735 patent. [3] All the claims of the '464 application were finally rejected by the examiner under section 102 of title 35, United States Code, and alternatively under section 103 of that title. Subsequently, an appeal (Appeal No. 424-40) was taken to the Board [4] which affirmed the examiner's rejections. Additionally, the Board entered a new rejection under 35 U.S.C. § 103 over a combination of references not previously cited by the examiner. In accordance with 37 C.F.R. § 1.196(b) (1985) [5], appellant elected reconsideration of the '464 application by the examiner. The examiner maintained the rejection entered by the Board; in Appeal No. 480-01, the Board affirmed the examiner. The Board's decision was appealed to the Court of Customs and Patent Appeals (CCPA). Upon the motion of the Commissioner of Patents and Trademarks and on the authority of

In re Dien, 680 F.2d 151, 214 USPQ 10 (CCPA 1982), the appeal was dismissed for lack of subject matter jurisdiction. [6]

The reissue application was protested by Biocraft Laboratories, Inc. (Biocraft), intervenor in the current appeal. Biocraft is also the plaintiff in a related litigation pending in the U.S. District Court for the District of New Jersey in which the validity and infringement of the '735 patent is in issue. *See Biocraft Laboratories Inc. v. Merck & Co.,* Civil Action No. 77-0693 (D.N.J.). The district court has stayed further action in that case pending the final outcome of the pending PTO proceedings.

C. *Reexamination Proceeding*

Following dismissal of the reissue appeal by the CCPA, Merck & Co., Inc. (Merck), the assignee of the '735 patent, filed for and was granted a request for reexamination of the patent. As a result of prosecution before the examiner, claims 1 through 3 of the reexamination application were finally rejected under 35 U.S.C. § 102 as anticipated by prior art references; the claims were also rejected under 35 U.S.C. § 103 as being obvious over references cited by the Board in its new ground of rejection entered during the initial reissue appeal. Finding the '735 patent to be entitled to the benefit of the November 30, 1959 filing date of its parent application, Serial No. 855,981, the Board reversed the section 102 rejection because the effective filing date of the application antedated all the references cited therein. The Board, however, sustained the rejection for obviousness under section 103. Expressly adopting the reasonings of its earlier reissue opinions, the Board took the position that in view of the prior art, in combination, and a thorough knowledge of the investigative techniques used in the medicinal chemical art, the skilled artisan would have expected the known tricyclic compound, amitriptyline, to be useful as an antidepressant.

D. *The References*

The references relied upon by the Board were:

(1) Rey-Bellet et all (Rey-Bellet) U.S. Patent No. 3,384,663, May 21, 1968 (application filed Mar. 27, 1959);

(2) Kuhn, *Schweizerische Medizinische Wochenschrift,* Vol. 87, No. 35-36, pp. 1135-1140 (Aug. 1957)

(3) Lehman et al. (Lehman), *Canadian Psychiatric Association Journal,* "The Treatment of Depressive Conditions with Imipramine (G 22355)", vol. 3, No. 4, pp. 155-164 (Oct. 1958);

(4) Friedman, *First Symposium On Chemical Biological Correlation,* "Influence of Isosteric Replacements Upon Biological Activity", pp. 296-358 (May 1950);

(5) Burger, *Journal of Chemical Education,* "Rational Approaches to Drug Structure", Vol. 33, No. 8, pp. 362-372 (Aug. 1956);

(6) Petersen et al. (Petersen), *Arzneimittel-Forschung,* Vol. 8, No. 7, pp. 395-397 (1958);

(7) Roche Research Report No. 43,162, pp. 1-9 (Nov. 1957);

(8) Roche Research Report No. 43,169, pp. 1-8 (Apr. 1958);

(9) Roche Research Report No. 52,195, pp. 1-13 (Sept. 1958) (Collectively called the "Roche Reports").

The Rey-Bellet patent disclosed amitriptyline and its hydrochloride salt. Properties of amitriptyline

taught by the reference included a "manifold activity upon the central nervous system," as well as pharmacological and medicinal properties, such as "narcosis-potentiating, adrenolytic, sedative, antihistaminic, antiemetic, antipyretic and hypothermic." Rey-Bellet did not disclose or otherwise teach that amitriptyline possessed antidepressive properties.

The Kuhn publication disclosed the compound, imipramine, and taught that the compound was a very effective antidepressant in humans. Imipramine has the chemical structure
Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

and differs from the structure of amitriptyline only in the replacement of the unsaturated carbon atom in the center ring with a nitrogen atom. Kuhn taught a recommended dosage of 75-150 mg per day -- possibly 200-250 mg if the smaller doses proved ineffective.

The Lehman publication disclosed the results of a Canadian study of the effects of imipramine on the symptons of depression in humans. This article confirmed, for the most part, the teachings of the Kuhn article.

The object of the Freidman publication was "to survey the history of isosterism, to classify the varieties of isosteric replacements which are recorded in the literature, and to note the influence of these replacements on the biological activity of compounds." Friedman defined isosteres as atoms, ions or molecules in which the peripheral layers of electrons can be considered identical. Compounds which fit this broad definition and exhibit the same biological activity were termed "bioisosteric." Further, with respect to the medicinal chemists' use of the theory of "isosteric replacement" or "bio-isosteric replacement" as a tool to predict the properties of compounds, Friedman commented that:

> [t]o the synthetic organic chemist interested in medicinal chemistry, every physiologically active compound of known structure is a challenge - a challenge either to better it, or perhaps merely to equal it. . . .
>
> There are numerous ways of attacking such a problem. . . . One of the methods which has been used frequently, very often with success, is that of isosteric replacement. The examples of this type of replacement in the literature are very numerous, and the fruitful results in the fields of sulfonamides, antimetabolites, and antihistamines are well known.

Friedman at page 296. Finally, Friedman disclosed various atoms or groups of atoms as bioisosteric, including the interchange of oxygen and the unsaturated carbon atom which often resulted in similar biological activity. Friedman, however, did not disclose or otherwise teach as bioisoteric the interchange of the nitrogen and unsaturated carbon atoms.

The Burger publication also discussed the theory of "bioisosterism" and its usefulness in designing new drugs based upon the knowledge of "lead" compounds.

The Petersen publication taught, *inter alia,* the properties of chlorpromazine (a phenothiazine derivative) and chlorprothixene (a 9-amino-alkylene-thioxanthene derivative), these compounds have the following structural formulas:
Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

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Petersen concluded that, when the nitrogen atom located in the central ring of the phenothiazine compound is interchanged with an unsaturated carbon atom as in the corresponding 9-amino-alkylene-thioxanthene compound, the pharmocological properties of the thioxanthene derivatives resemble very strongly the properties of the corresponding phenothiazines. Using the theory of isosteric replacement, Petersen predicted this similarity in properties:

> Structural chemical considerations permitted the expectation that the 9-aminoalkylene-thioxanthenes . . . would show great similarity to the corresponding phenothiazines. They should be more similar in their behavior to that of the phenothiazines than the saturated 9-aminoalkyl-thioxanthenes. From the physical point of view the p- electron distributions (sites of p - electrons) are almost the same in the phenothiazine derivatives and in the 9-aminoalkylene-thioxanthenes with their stabilizing conjugated double linkage between C9 in the thioxanthene ring and the first C-atom of the side chain.

Petersen at page 3. The compounds were disclosed as having a strong central depressive, i.e., tranquillizing, action in animals.

The Roche Reports revealed the results from tests comparing the pharmacological properties of amitriptyline and imipramine. The reports indicated that the two compounds were very similar in a variety of properties, including their action as tranquilizers having narcosis-potentiating effects. Because of this similarity and because amitriptyline and imipramine were structurally related, Roche scientists concluded that amitriptyline should be clinically tested for depression alleviation -- a known property of imipramine. In the pharmalogical guideline for the clinical testings of amitriptyline (which was labelled Roche Preparation Ro 4-1575), the Roche Reports stated that

> [i]t is to be noted that a "tofranil-like effect" is already to be expected by using a dose ¼ -- ½ that of Tofranil. Side effects which can appear . . . are sedative and atropine-like effects, such as appear also with Tofranil. [7]

We must decide in this appeal whether appellant's invention would have been prima facie obvious over the available prior art of record; and, if so obvious, whether the prima facie case has been rebutted by evidence of unexpected results.

III. DISCUSSION

In its opinion on this problem, the Board expressly followed the guidelines of *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 466-67 (1966), and made findings on factual inquiries specifically set forth in that decision. These factual findings must be accepted unless they are clearly erroneous. *In re Wilder,* 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984), *cert. denied,* 105 S.Ct. 1173 (1985); *In re De Blauwe,* 736 F.2d 699, 703, 222 USPQ 191, 193 (Fed. Cir. 1984); *accord Stock Pot Restaurant, Inc. v. Stockpot, Inc.,* 737 F.2d 1576, 1578-79, 222 USPQ 665, 666-67 (Fed. Cir. 1984). In this case we do not hold the Board's factual findings -- as to the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the art -- to be clearly erroneous and accordingly we have followed them in our statement of the prior art and we now follow them in our analysis of the legal issue of obviousness.

Prima Facie Obviousness: The prior art taught that amitriptyline and imipramine are both psychotropic drugs which react on the central nervous system and which were known in the art prior to the time of appellant's invention. Imipramine was known to possess antidepressive properties in humans. While amitriptyline was known to possess psychotropic properties such as sedative and narcosis-potentiating properties, the drug was not known to be an antidepressant. However, the prior art has shown that imipramine and amitriptyline are unquestionably closely related in structure. Both compounds are tricyclic dibenzo compounds and differ structurally only in that the nitrogen atom located in the central ring of imipramine is interchanged with an unsaturated carbon atom in the central ring of amitriptyline. To show obviousness, it was necessary to determine from knowledge

already available in the art at the time of appellant's invention that one skilled in the medicinal chemical art would have expected amitriptyline, like imipramine, to be useful in the treatment of depression in humans. *In re*

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Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

As found by the Board, the Roche Reports recognized the structural relationship between amitriptyline and imipramine and concluded that amitriptyline should be tested for its anti-depressant activities. In fact the Roche Reports expressly stated that amitriptyline was expected to resemble imipramine clinically in its depression alleviation effects.

"Structural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties." *In re Payne,* 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). However, the Board did not rest its conclusion of obviousness on structural similarity alone. Rather, the Board further recognized that in attempting to predict the biological activities of a drug, a skilled medicinal chemist would not proceed randomly, but would base his attempts on the available knowledge of prior research techniques, and literature used in his field. The prior art showed that one such technique was "bioisosteric replacement" or the theory of bioisosterism -- where the substitution of one atom or group of atoms for another atom or group of atoms having similar size, shape and electron density provides molecules having the same type of biological activity. Finding that the Friedman, Burger and Petersen references taught that bioisosterism was commonly used by medicinal chemists prior to 1959 in an effort to design and predict drug activity, the Board concluded that one of ordinary skill in the arts would have been aware of this technique at the time of appellant's invention. [8] Further, the Board found that Petersen taught as bioisosteric the interchange of the nitrogen and unsaturated carbon atoms -- the precise structural difference between imipramine and amitriptyline. [9]

We see no clear error in the Board's determination as to the teachings of the prior art references, in combination. In view of these teachings, which show a close structural similarity and a similar use (psychotropic drugs) between amitriptyline and imipramine, one of ordinary skill in the medicinal chemical arts, possessed of the knowledge of the investigative techniques used in the field of drug design and pharmacological predictability, would have expected amitriptyline to resemble imipramine in the alleviation of depression in humans. Accordingly, we agree with the Board that appellant's invention was prima facie obvious over the prior art of record.

In traversing the Board's decision of obviousness, appellant has urged that the Board's decision was premised on an impermissible "obvious to try" standard. Appellant contends that there was no motivation in the prior art to arrive at appellant's invention. "[O]bvious to try is not the standard of 35 U.S.C. § 103." *In re Antonie,* 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977) (emphasis omitted). Rather, the test is whether the references, taken as a whole, would have suggested appellant's invention to one of ordinary skill in the medicinal chemical arts at the time the invention was made. *In re Simon,* 461 F.2d 1387, 1390, 174 USPQ 114, 116 (CCPA 1972). Clearly, amitriptyline and imipramine, both known psychotropic drugs, are closely structurally related. The expectation that the similar structures would behave similarly was suggested in the Roche Reports. In combination with those teachings, the prior art teaching that the precise structural difference between amitriptyline and imipramine involves a known bioisosteric replacement provides sufficient basis for the required expectation of success, without resort to hindsight. [10] Obviousness does not require absolute predictability. *In re Lamberti,* 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976). Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness. *In re Longi,*

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759 F.2d 887, 897, 225 USPQ 645, 651 (Fed. Cir. 1985).

We also find untenable appellant's arguments that Petersen teaches away from appellant's invention. Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. *In re Keller,* 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Thus, Petersen must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole. That teaching is that the interchange of the nitrogen and the unsaturated carbon atoms is isosteric and compounds so modified are expected to possess similar biological properties.

Neither are we persuaded by appellant's contention that the Board erred in relying on the contemporaneous independent invention of others to support its holding of obviousness. [11] As we have said earlier, the teachings of the prior art references in combination adequately support the Board's conclusion. However, the additional, although unnecessary, evidence of contemporaneous invention is probative of "the level of knowledge in the art at the time the invention was made." *In re Farrenkopf,* 713 F.2d 714, 720, 219 USPQ 1, 6 (Fed. Cir. 1983).

Unexpected Results: A prima facie case of obviousness can be rebutted by evidence of unexpected results. *In re Davis,* 475 F.2d 667, 670, 177 USPQ 381, 384 (CCPA 1973). In rebuttal of the PTO's prima facie case appellant has asserted that, as compared to imipramine, amitriptyline unexpectedly has a more potent sedative and a stronger anticholinergic effect. In support of this contention, appellant has relied on an affidavit of Dr. Joseph J. Schildkraut, [12] a psychiatrist and a Professor of Psychiatry at Harvard, and also on a published record of a symposium of physicians and psychiatrists concerned with the treatment of the depressed patient. [13]

Dr. Schildkraut's affidavit recognizes some pharmacological differences between amitriptyline and imipramine including the fact that amitriptylne is a more potent sedative and has a strong anticholinergic effect than imipramine. Further, Dr. Schildkraut notes that depressed patients have responded differently to amitriptyline and imipramine, some responding to one and not the other or more favorably to one than to the other. For the most part, the record of the cited symposium confirms the differences noted in the Schildkraut affidavit. [14] That record also counseled practicing physicians on choosing from the spectrum of tricyclic antidepressants (a term which includes amitriptyline and imipramine) the particular drug useful for an individual patient.

After a careful consideration of all the evidence, we are persuaded that the Board did not err in determining that the alleged unexpected properties of amitriptyline are not so unexpectedly different from the properties of imipramine, the closest prior art, as to overcome the prima facie showing of obviousness. The prior art of record clearly taught that amitriptyline was a known sedative. [15] The evidence before us (which was, of course, before the Board) further revealed that all tricyclic antidepressant drugs, in general, possess the secondary properties of sedative and anticholinergic effects. Specifically, the record showed that during the prosecution of the reissue application, appellant submitted an article entitled "Using the tricyclic antidepressants" which included a table comparing the properties of known tricyclic antidepressant drugs. [16] Included in these properties were sedative and anticholinergic effects of the known antidepressants. [17] Thus, it appears that the alleged difference in properties between amitriptyline and imipramine is a matter of degre *e* r *a* ther than kind. Moreover, as to the sedative effects, the article revealed only a slight difference between the two compounds. Amitriptyline was characterized as "highly sedative" while imipramine was only "somewhat less [sedative] than amitriptyline." [18] Regarding

the anticholinergic effect, the article showed that both drugs have anticholinergic effects but to a different degree. These are not truly unexpected results. The Board found in one of its reissue opinions (incorporated in the reexamination decision now on appeal): "[i]n regard to the sedative and anticholinergic properties of amitriptyline, we are not convinced that the side effects of this material [amitriptyline] are significantly or unexpectedly different from the level of those properties exerted

by the closest prior art antidepressant, imipramine. [19]

The core of it is that, while there are some differences in degree between the properties of amitriptyline and imipramine, the compounds expectedly have the same type of biological activity. In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the prima facie case. The fact that amitriptyline and imipramine, respectively, helped some patients and not others does not appear significant. As noted by the Board, a difference in structure, although slight, would have been expected to produce some difference in activity.

[1] In sum, we hold that the claimed invention would have been obvious to one of ordinary skill in the art. Accordingly, the decision of the Board is

AFFIRMED.

Footnotes

Footnote 1. *Ex Parte Merck and Co.,* Reexamination No. 90/000264, Appeal No. 607-66 (PTO Bd. Pat. App. & Int., May 28, 1985), JA p.7. In its opinion the Board expressly adopted the reasonings in its earlier reissue (for the '735 patent) opinions, *Ex Parte Edward L. Engelhardt,* Reissue Application No. 776,464, Appeal No. 424-40 (PTO Bd. Pat. App., Apr. 23, 1980), JA p. 13 and *Ex Parte Edward L. Engelhardt,* Reissue Application No. 776, 464, Appeal No. 480-01 (PTO Bd. Pat. App., Fed. 25, 1982), JA p. 23.

Footnote 2. U.S. Patent No. 3,428,735, issued to Edward L. Engelhardt on February 18, 1969, was based on patent application Serial No. 662,907 filed August 24, 1967 as a continuation-in-part of patent application Serial No. 855,981 filed Nov. 30, 1959.

Footnote 3. The reissue application was filed as a "no defect" type reissue under the then existing 37 C.F.R. § 1.175(a)(4) (1980). That provision has now been repealed.

Footnote 4. At that time, the Board of Patent Appeals and Interferences was called the Board of Patent

Footnote 5. 37 C.F.R. § 1.196(b) provides that when the Board of Appeals determines a new ground of rejection, the appellant may

> (1) after submitting appropriate amendments or showing of facts, have the matter reconsidered by the examiner;
>
> (2) waive reconsideration before the examiner and have the case reconsidered by the Board; or
>
> (3) treat the decision, including the new ground of rejection, as a final decision in the case.

Footnote 6. *See In the Matter of the Application of Edward L. Engelhardt,* Appeal No. 82-611 (CAFC Oct. 28, 1982) (order granting motion to dismiss).

Footnote 7. Tofranil is a tradename used for imipramine.

Footnote 8. Appellant submitted the declaration of Dr. Paul N. Craig, an experienced medicinal chemist, JA p. 372. His view was that the concept of bioisosterism could not be used in 1959 to predict the antidepressant effects in amitriptyline or the pharmacological differences between imipramine and amitriptyline. Dr. Craig stated:

> [I]n my opinion "isosterism" in 1959 afforded no basis for predicting the specific pharmaceutical utility in humans, and it is my belief that that is still true today . . . . I do not believe the carryover of tranquilizing activity from chlorpromazine to chlorprothixene afforded a reasonable basis for predicting the carryover of antidepressant properties from imipramine to amitriptyline.

Affidavit of Paul N. Craig, JA, pp. 374-75.

Plainly the Board was not clearly erroneous in discounting that testimony. There was independent evidence in the record to the contrary. The Friedman, Burger and Petersen references recognize that concept as a means of predicting biological properties in isosterically-related compounds prior to 1959.

Footnote 9. Petersen even went so far as to suggest that the apparent bioisosteric relationship between the interchange of the nitrogen and unsaturated carbon atoms led to the design of chloroprothixene in the expectation that the compound would share the same biological activity as chlorpromazine. *See* Petersen, *supra,* at p. 395.

Footnote 10. The teachings of the Roche Reports as well as the Petersen reference distinguish this case from *In re Grabiak,* 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("there is no motive in the cited art to make the modification required to arrive at appellants' compounds").

Footnote 11. *Ex Parte Edward L. Engelhardt,* Appeal No. 424-40, *supra* note 1, at pp. 23-24, JA pp. 22(l)-22(m), where the Board indicated that evidence before it revealed that four other groups of inventors independently and contemporaneously discovered amitriptyline's antidepressant properties using reasoning based on a thorough knowledge of investigative techniques, which included the concept of isosterism, used in the medicinal art area.

Footnote 12. Affidavit of Joseph J. Schildkraut, JA p.

Footnote 13. Symposium, *Depression Today -- Experts Answer Your Questions,* JA p.

Footnote 14. Dr. Schildkraut was a member of the

Footnote 15. Rey-Bellet, *supra,* col. 2, line 16.

Footnote 16. *Patient Care,* "Using the Tricyclic Antidepressants," pp. 28-33, 39-40, 43-45, 49-52, 57-58, 63-64, 67-68, 71, 75-76, 78, 81 84-85, (May 15, 1979); *see also* Commission's Appendix, pp. CA 17-45.

Footnote 17. *See also* the Symposium, *Depression Today -- Experts Answer Your Questions, supra,* note 13, at p. 315, where Dr. Hollister indicates that when choosing from the spectrum of tricyclic antidepressant drugs, the choice is based on three pharmocological actions including (1) the amount of sedation (2) the amount of anticholinergic effect and (3) the nature of the drugs in primarily blocking the uptake of serotin or norepinephrine.

Footnote 18. *Patient Care,* "Using The Tricyclic Antidepressants," *supra* note 16, at p.

Footnote 19. *Ex Parte Edward L. Engelhardt,* Appeal No. 480-01, supra note 1, at p.12 JA p.

Dissenting Opinion Text

Dissent By:
Baldwin, Circuit Judge, dissenting.

The rejection by the board is flawed because it did not analyze the invention according to the requirement of 35 U.S.C. § 103. The board wrote:

> The issue before us in considering the instant claims on their merits for patentability is whether the artisan having the requisite skill in the pertinent art area and a knowledge of the available prior art would have been motivated to employ amitriptyline in the treatment of human depression.

That is, whether it would have been obvious to try amitriptyline as an antidepressant. Guided by the disclosure of the applicant, the board pieced together information from various patents, journal articles, and papers, and concluded:

> It remains our position that one having ordinary skill in this art are [sic] would have been familiar with the concept of bioisosterism and because of this knowledge would have concluded that the known compound, i.e., amitriptyline, would be *potentially* useful as an antidepressant. [Emphasis ours.]

That is, it would have been obvious to try amitriptyline as an antidepressant. Obvious-to-try is not the test for patentability under 35 U.S.C. § 103. This court and its predecessor, the CCPA, have repeatedly rejected that approach. *In re Godwin,* 576 F.2d 375, 377, 198 USPQ 1, 3 (CCPA 1978); *In re Antoine,* 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977); *In re Lindell,* 385 F.2d 453, 455, 155 USPQ 521, 523 (CCPA 1967); *In re Tomlinson,* 363 F.2d 928, 150 USPQ 623 (CCPA 1966); *In re Papesch,* 315 F.2d 381, 137 USPQ 43 (CCPA 1963); *see also In re Grabiak,* 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985).

Congress has also rejected that approach by enacting the second sentence of 35 U.S.C. §103, which states "[p]atentability shall not be negatived by the manner in which the invention was made." The reviser's note on this sentence states "it is immaterial whether it resulted from long toil and experimentation or from a flash of genius."

The obvious-to-try analysis is an attack on the method of making an invention that specifically penalizes people in areas of endeavor where advances are won only by great effort and expense. The pharmaceutical field is particularly hard hit because there is an over abundance of structures that are obvious to try. Consider, for example, the Peterson reference which the majority cites to demonstrate the possibility that a nitrogen atom may be replaced by a double-bonded carbon atom. This journal article records an attempt to find drugs useful for the treatment of endogenous psychoses, i.e., tranquilizers. The researchers tested eighteen chemicals with closely related structures. These materials were injected into mice, and compared for their ability to make the mice fall asleep. The results of these may be tantalizing and useful, but only as a guide for further research. I agree that, based on this information and the other references cited by the board, the researcher with ordinary skill in the art would be motivated to investigate the possibility of substituting a double-bonded carbon atom for nitrogen. The researcher would also be motivated to test every other structural variation in Peterson, as well as a host of others. Under an obvious-to-try analysis, any of these structures which ultimately is shown to be effective as an antidepressant in human beings would be unpatentable because the researcher dared to follow a logical plan.

The board and the majority also err by reading too much certainty into the teachings of the references. They have not considered the references as a whole. Friedman discusses the phenomenon that compounds with similar chemical structures sometimes behave in a similar fashion in a biological system. Once such a compound has been tested and found to have the same biological activity, it is called "bio-isosteric." [1]

Friedman also teaches that an isosteric compound "may have the same activity as the original, *or*

more usually it may have an *antagonistic* effect." (Emphasis added.) Friedman explains that in order to predict biological activity with accuracy, one ideally should know (1) the mechanism by which the original drug acts and (2) what part of the structure of the original drug is critical to the original drug activity. [2] That reference also unequivocally states that comparisons should be made in living systems, but such information is not easily available. That reference relies on *in vitro* testing, and it specifically states that *in vitro* results may or may not correlate with clinical studies. It also clearly states that, for the purposes of its discussion, biological activities such as absorption, distribution, conjugation (detoxification), taste, odor and *side effects of drugs* will be ignored. Friedman concludes that compounds with similar structures need not be bio-isosteric.

The Burger reference does discuss bio-isosterism and its usefulness in designing new drugs. Its evaluation of bio-isosterism as a tool for predicting drug activity is as follows:

> However, if one can achieve a gradual change of biological behavior and follow it accurately at each step of minor structural alteration, one is bound to enhance one property, suppress another, and ultimately arrive at a drug suitable for therapy. Shortcuts to this disconcertingly tedious process have not been found, and this is probably responsible for the still prevailing opinion that new useful drugs will be discovered most easily by more or less empirical procedures.

at page 369, and

> Slight sterochemical or structural changes may alter considerably the biological role of a compound. Patient variation of at least a reasonable number of structures is still the only answer to this question.

at page 370.

The Roche reports contain background information about various pharmacological effects of amitriptyline. The information was derived from testing for its toxicity and tranquilizing effect on animals. This information would be essential to a decision to clinically test the drug. It is not sufficient to show the drug would be useful for treating human beings. Congress gave pragmatic recognition to the difficulty of determining whether a new drug is useful by its enactment of the 1962 amendment to 21 U.S.C. § 321. That action was taken in response to problems caused by another tranquilizer, thalidomide.

Neither these references, nor the other references cited by the board and the majority purport to teach the worker with ordinary skill in the art that amitriptyline is a drug that is useful for treating depression in human beings. That conclusion is steps removed from the information presented by these sources. I would reverse.

Footnotes

Footnote 1. The term "bio-isosteric" therefore is simply a conclusion drawn after testing. The label is properly limited to the system and purpose for which the compounds were tested. For example, two drugs could be bio-isosteric with respect to making mice fall asleep, and not bio-isosteric when tested at a particular dosage level for the treatment of high blood pressure in human beings. The theory of bio-isosterism as used by the board and majority is nothing more or less than an analysis of structural obviousness.

Footnote 2. Neither this reference nor any of the others purport to disclose either piece of

- End of Case -

Print-Friendly Version

FULL TEXT OF CASES (USPQ2D)
All Other Cases
In re Vaeck (CA FC) 20 USPQ2d 1438 (10/21/1991)

In re Vaeck (CA FC) 20 USPQ2d 1438

In re Vaeck

U.S. Court of Appeals Federal Circuit
20 USPQ2d 1438

Decided October 21, 1991
No. 91-1120

Headnotes

PATENTS

1. Patentability/Validity - Obviousness - Combining references (§ 115.0905)

Rejection of claimed subject matter as obvious under 35 USC 103 in view of combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that such person would have reasonable expectation of success; both suggestion and reasonable expectation of success must be founded in prior art, not in applicant's disclosure.

2. Patentability/Validity - Obviousness - Relevant prior art - Particular inventions (§ 115.0903.03)

Patent and Trademark Office has failed to establish prima facie obviousness of claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, since prior art does not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill reasonable expectation of success in doing so; expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious expression of unrelated genes in cyanobacteria for unrelated purposes.

3. Patentability/Validity - Specification - Enablement (§ 115.1105)

JUDICIAL PRACTICE AND PROCEDURE

Procedure - Judicial review - Standard of review - Patents (§ 410.4607.09)

Specification must, in order to be enabling as required by 35 USC 112, first paragraph, teach person skilled in art to make and use invention without "undue experimentation," which does not preclude some experimentation; enablement is question of law which is reviewed independently on appeal, although such determination is based upon underlying factual findings which are reviewed for clear error.

PATENTS

4. Patentability/Validity - Specification - Enablement (§ 115.1105)

Patent and Trademark Office did not err in rejecting, as non-enabling pursuant to 35 USC 112, first paragraph, claims for use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitos and black flies, in view of relatively incomplete understanding of biology of cyanobacteria as of applicants' filing date, as well as limited disclosure by applicants of particular cyanobacterial genera operative in claimed invention, since there is no reasonable correlation between narrow disclosure in applicants' specification and broad scope of protection sought in claims encompassing gene expression in any and all cyanobacteria.

Case History and Disposition:

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Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent, serial no. 07/021,405, filed March 4, 1987, by Mark A. Vaeck, Wipa Chungjatupornchai, and Lee McIntosh (hybrid genes incorporating a DNA fragment containing a gene coding for an insecticidal protein, plasmids, transformed cyanobacteria expressing such protein and method for use as a biocontrol agent). From decision rejecting claims 1-48 and 50-52 as unpatentable under 35 USC 103, and rejecting claims 1-48 and 50-51 for lack of enablement, applicants appeal. Affirmed and part and reversed in part; Mayer, J., dissents with opinion.

Attorneys:
Ian C. McLeod, Okemos, Mich., for appellant.

Teddy S. Gron, associate solicitor (Fred E. McKelvey, solicitor and Richard E. Schafer, associate solicitor, with him on brief), for appellee.

Judge:
Before Rich, Archer, and Mayer, circuit judges.

Opinion Text

Opinion By:
Rich, J.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 USC 103, as well as the rejection of claims 1-48 and 50-51 under 35 USC 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

BACKGROUND

A. *The Invention*

The claimed invention is directed to the use of genetic engineering techniques 1 for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus* proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.

As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote 2 kingdom, the

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cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within transformed 3 cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.

More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing 4 the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.

The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:

1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:

(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and

(b) at least one DNA fragment coding for an insecticidally active protein produced by a Bacillus strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,

the DNA fragments being linked so that the gene is expressed.

Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers. 5 Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which expresses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

B. *Appellants' Disclosure*

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus* (*B. thuringiensis, B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis, Anacystis, Synechococcus, Agmenellum, Aphanocapsa, Gloecapsa, Nostoc, Anabaena* and *Ffremyllia*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis,* linked to (2) a particular promoter, the P_L promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P_L promoter.

C. *The Prior Art*

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns, 6 the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT). 7 Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

Sekar I, 8 Sekar II, 9 and Ganesan 10 collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium, B. subtilis* and *E. coli.*

Friedberg 11 discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the $O_L P_L$ operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed,

highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis* ...."

Miller 12 compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases 13 purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli.*

Nierzwicki-Bauer 14 identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbc* L, the large subunit of the enzyme ribulose-1, 5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.

Chauvat 15 discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

Reiss 16 studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

Kolowsky 17 discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.

Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

D. *The Grounds of Rejection*

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 USC 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus,* and the advantages of expressing such genes in heterologous 18 hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the

expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was prima facie obvious.

Additional rejections were entered against various groups of dependent claims which we need not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above.

The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 USC 112, first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) 19 and (z) 20 as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided in the specification. With respect to unpredictability, the examiner stated that

he cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis, Anacystis, Synechococcus, Agmenellum, Nostoc, Anabaena,* etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera. Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970)."

OPINION

A. *Obviousness*

We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 USC 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff,* 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990).

[1] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

[2] We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in

cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli.* While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed *bacterial* hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae. 21 Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell,* this court affirmed an obviousness rejection of a claim to a method for

producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 USPQ2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 USPQ2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.

....

... Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 USPQ2d at 1679-80.

In contrast with the situation in *O'Farrell,* the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. *Enablement*

[3] The first paragraph of 35 USC 112 requires, *inter alia,* that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 USPQ2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 USPQ2d at 1402.

In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

[4] Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the

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Hodosh v. Block Drug Co., Inc.

(CA FC)
229 USPQ 182

Decided March 24, 1986
No. 85-2607
U.S. Court of Appeals Federal Circuit

Headnotes

PATENTS

1. Patentability -- Invention -- Specific cases -- Chemical (§ 51.5093)

Summary judgment holding that claimed tooth desensitizer was invalid for obviousness was improper, in view of existing questions of material fact concerning various terms used in Chinese and European references.

2. Patentability -- Invention -- In general (§ 51.501)

Secondary considerations and additional evidence likely to be considered at trial must be considered in obviousness determination.

Particular patents -- Dental Treatments

3,863,006, Hodosh, Method for Desensitizing Teeth, holding of invalidity reversed.

Case History and Disposition:

Appeal from District Court for the District of New Jersey, Sarokin, J.; 226 USPQ 645 .

Action by Milton Hodosh, and Richardson-Vicks, Inc., against Block Drug Company, Inc., and Dentco, Inc., for patent infringement. From summary judgment for defendants, plaintiffs appeal. Reversed and remanded.

Attorneys:

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Jerome G. Lee, and Morgan, Finnegan, Pine, Foley & Lee, both of New York, N.Y. (William S. Feiler, Maria C.H. Lin, Morgan, Finnegan, Pine, Foley & Lee, Marvin C. Soffen, Edward A. Meilman, and Ostrolenk, Faber, Gerb & Soffen, all of New York, N.Y., on the brief) for appellees.

Judge:
Before Rich, Davis, and Baldwin, Circuit Judges.

Opinion Text

Opinion By:
Rich, Circuit Judge.

This appeal is from the July 12, 1985, judgment of the United States District Court for the District of New Jersey, 226 USPQ 645 , granting summary judgment to Block Drug Company, Inc., et al. (Block) and holding that all six claims of patent No. 3,863,006 for "Method of Desensitizing Teeth" ('006 patent), issued to Dr. Milton Hodosh and licensed to Richardson-Vicks, Inc. (collectively, Hodosh), are invalid for obviousness under 35 USC 103. We reverse remand.

Background

Tooth desensitizers reduce discomfort and pain caused by tooth hypersensitivity or exposed dentin, the portion of the tooth between the enamel and the pulp which includes a myriad of microscopic tubules. Persons suffering from this condition react painfully to hot or cold foods, citric acid or sweets, or everyday chemical, thermal, or tactile stimuli including toothbrush contact.

Milton Hodosh, a practicing dentist for about thirty years, independently developed the claimed subject matter of the '006 patent and granted Richardson-Vicks an exclusive license to make, use, and sell the claimed invention; the latter markets its tooth desensitizing toothpaste under the trademark "Denquel."

Claim 1 of the '006 patent [1] reads:

> The method of desensitizing hypersensitive dentin and cementum by applying thereto an agent the essential ingredient of which is a nitrate of one of the following alkali metals: potassium, lithium or sodium said nitrate comprising between 1 percent and 20 percent by weight of said agent.

The remaining claims appear in the opinion below.

Appellee Block has, since 1961, marketed a tooth desensitizing toothpaste, covered by its patent No. 2,122,483 (the Rosenthal patent) for "Strontium Ion Toothpaste" issued in 1964, under the trademark "Sensodyne." The Rosenthal patent and the '006 patent disclose toothpaste formulae which are the same except that the latter contains, as a desensitizing agent, potassium nitrate instead of the Rosenthal-Block strontium chloride. After requesting and being denied a license under the '006 patent, Block developed its own potassium nitrate-containing tooth-desensitizing toothpaste called "Promise" and "Sensodyne-F." [2]

March 30, 1983, Hodosh sued Block alleging that the sale of "Promise" and "Sensodyne-F"

contributorily infringed and actively induced infringement of the '006 patent. Block answered and counterclaimed alleging patent misuse and consequent unenforceability of the '006 patent. On July 11, 1984, Block moved for summary judgment as to both misuse and patent invalidity. Oral argument was heard October 16, 1984, and decision was reserved. June 14, 1985, the reported decision was handed down granting the motion as to patent invalidity and dismissing the motion on misuse as moot, resulting in the judgment now on appeal.

The district court heard no expert testimony, but did hear arguments of counsel, receive briefs, review exhibits, and had before it declarations and affidavits from experts on both sides commenting on the eight prior art references involved here, including the Rosenthal patent. The court determined that there were no genuine issues of material fact and concluded as a matter of law that the claims of the '006 patent were invalid under §103 because the Rosenthal patent disclosed each element claimed in the '006 patent except the potassium nitrate, which, in its view, was disclosed in two Chinese references, both based on ancient Chinese writings. The court also stated that six European references supported its conclusion of obviousness.

Because the appropriateness of summary judgment is determined on an analysis of the facts, *First National Bank of Arizona* v. *Cities Service Co.,* 391 U.S. 253 (1968), and because everything about these references, as a whole, *see, e.g., Interconnect Planning Corp.* v. *Feil,* 774 F.2d 1132, 1138, 227 USPQ 543, 547-48 (Fed. Cir. 1985), is important to our determination, we review the record and lay out the relevant portions of the references in some detail.

A. *The Chinese References*

1. *The Grand Dictionary of Chinese Medicine and Drugs*

(The Grand Dictionary)

The *Grand Dictionary,* published in Hong Kong in 1963 and written in Chinese, is based on ancient Chinese compilations assembled roughly 500 years ago from works of physicians going back 4000-5000 years. Only a portion of the 1963 Chinese text was before the court and is before us on appeal. For purposes of this litigation, that portion was translated into English by Block's translator, Roger Wei-Ming Tsao (Mr. Cao). Mr. Cao is a doctor of Chinese medicine and a bilingual tutor. Block's other expert, Dr. Stephen Wei, a professor of dentistry fluent in Chinese, concurred in that translation. The writings from which the *Grand Dictionary* was compiled are not in evidence nor are any earlier writings.

In a nutshell, the district court relied upon the *Grand Dictionary* because of its discussion of "xiao shi" to which the Grand Dictionary associates the name "niter" and the chemical composition KNO_3 and the ability to cure, inter alia, tooth pain. The court's opinion was that this reference teaches the use of xiao shi, which is the same as niter and is therefore the same as potassium nitrate, to cure tooth pain; thus, the teachings of the Rosenthal patent and the *Grand Dictionary* show that the '006 invention would have been obvious.

The following discussion and quotations are part of an attempt to convey the nature of the *Grand Dictionary.* The translated portion of the *Grand Dictionary* is entitled "Niter." The text under the first subheading "Nomenclature" reads: "It was so named because it has the power to consume various stones." Under "Other Names Stated in Classical Medical Books," the text reads "Mang Xiao (Bie-Lu), Bitter Xiao (Zhen-Quan), Flaming Xiao (Tu-Su) . . . and Xiao-Shi . . . ." Thereafter, following "Foreign Names," the *Grand Dictionary* reads: "Salpetrae, Salnitri (in Latin); Niter (in English); and Salpoter (in German)." One page later, "KNO_3" is listed under "Chemical Composition."

The portion upon which Block and the district court rely to show that this substance cures tooth pain is headed "Collective Statements" and reads:

> (Ming): Li-Shi-Zhen said: It cures summer infections and the catching of colds. It cures acute enteritis with severe vomiting, exertion through excessive sexual activity, black jaundice, chronic abdominal pain, conjunctivitis, headaches and tooth pain.

The next three or so pages of the *Grand Dictionary* list the ailments that this substance cures. An interesting but not atypical paragraph reads: "For curing the paralysis of the four limbs, leprosy or problems caused by Taoist stone eating." This substance also apparently cures indigestion, lack of energy, typhoid, cataracts, and much, much more. The *Grand Dictionary* compares what appears to

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be various forms in which xiao shi is found, and the characteristics of each. An excerpt is:

> Pu-Xiao (Na_2SO_4) has the nature of water, tastes salty, and its flavor is cold. It can only descend and cannot ascend. It is Yin within Yin -- that's why it can cleanse the accumulation in the gastrointestinal tract and can expel the San-Jiao devilish fire. Whereas Niter (KNO3) has the nature of fire, tastes bitter and spicy, tastes slightly salty and has a flavor which is very warm, it's [sic] nature is ascending. It is fire within water. That's why it can break the accumulation and disperse hardness, and cure the febrile diseases.

2. *Ben Cao Gang Mu*

Ben Cao Gang Mu (Ben Cao) is a treatise on Chinese Medicine published in Hong Kong, in Chinese, in 1930, 1954, and 1965, but was originally written by Li-Shi-Zhen who lived during the Ming Dynasty. [3] Like the *Grand Dictionary,* only a portion of the Chinese text *Ben Cao* is in evidence and that portion was translated by Mr. Cao and Dr. Wei for purposes of this litigation. The district court relied upon *Ben Cao* because it discusses "xiao shi," which the translation of *Ben Cao* states is "niter" and associates the ability to cure "tooth pain (Ya Tong or Ya Teng)."

It is important to note, and the district court appeared to accept as fact, that the portion of the *Grand Dictionary* relied upon was compiled during the Ming Dynasty of the 13th to 15th centuries in *Ben Cao Gang Mu* so that the relevant portion of the *Grand Dictionary* is substantially a restatement of *Ben Cao* with some modification by an unidentified author. The court stated that these two references "quote the same Ming Dynasty source as labeling KNO_3 for tooth pain."

The *Ben Cao* translation is entitled "Xiao-Shi (Niter)" and refers to the same "Other names" for this substance listed in the *Grand Dictionary.* With respect to the quoted sections above, the *Ben Cao* translation is nearly verbatim. It has this to say about tooth pain:

> Da Ming states: It cures summer infections and the catching of colds, acute enteritis with severe vomiting, exertion thru excessive sexual activity and black jaundice, chronic abdominal pain, conjunctivitis, headache and tooth pain (Ya-Tong or Ya Teng).

Hodosh argues that summary judgment was inappropriate; issues of fact as to the meanings of xiao shi and ya tong remain because a skilled dental researcher would surely seek and obtain a complete translation of the *Grand Dictionary* and of the other ancient Chinese references and would read those references carefully. Hodosh also argues that the ancient references should be dismissed because a person skilled in the art would find them incredible and would regard them as a quagmire of medical and dental nonsense. It therefore takes issue with the court's holding quoted below which apparently precluded inquiry into the accuracy of the references by one skilled in the art:

> [A]ttacks upon the translation leading up to the prior art reference embodied in the *Grand Dictionary of Chinese Medicine and Drugs,* . . . or upon Chinese medicine as a whole, . . . are not here regarded as particularly pertinent, since they require skill beyond the scope of the "experienced researcher in dental fields . . . ."

Hodosh relies heavily on its expert's, Dr. Shklar's, testimony about the Chinese references: "[T]hey represent in modern terms, materials that are rarely comprehensible and frequently contradictory in their literal terms. The materials are largely seen by contemporary medical scientists as absurd; no serious medical researcher would waste his or her time with them." [4] Hodosh also contests this holding by the district court:

> Nor, if it is true that KNO_3 alleviates tooth sensitivity, is such reference in the prior art rebutted by the existence of errors in the reference such as, for example, the claim that KNO_3 is a cure for "exertion through excessive sexual activity." Whatever the merits of the other aspects of the Chinese references, the fact that they reveal KNO_3 to be a cure for ya tong is what is dispositive here. The reference clearly discloses such function of potassium nitrate, albeit in the context of otherwise incredible, and even erroneous descriptions of the compound's quality.

With respect to the specific meaning of xiao shi as used in these references, both Dr. Shklar and Hodosh's other expert, Mr. Yen, a professional translator of Chinese and English lan

guages, stated that the compiler of the *Grand Dictionary* erred in associating potassium nitrate or niter with xiao shi. Mr. Yen states that he

> was not able to render one single precise version because various dictionaries contain different and even conflicting definitions. For example, *Source of Words,* a Chinese language dictionary, published by Commercial Press, Taiwan, which has editions dating back to 1915, defines "Xiao-Shi" as "Mang-Xiao" on page 1255, and under "Mang-Xiao" on page 1770, reference is made that "Mang-Xiao" is "Liu-Suen-Na," and on page 1523 "Liu-Suen-Na" is defined as sodium sulfate ($Na_2SO_4 10H_2O$).

Mr. Yen also stated that "Xiao-Shi could be more than one material and that more than one material may be represented by the term 'Xiao-Shi'."

Dr. Shklar concurred:

> In my opinion, therefore, the answer to the question: What was "Xiao-Shi," is that it represented many different materials which cannot be identified with certainty.
>
> Thus, these Exhibits did not describe potassium nitrate to one skilled in the art any more than any of the hundreds of salts, ores and oxides that possess some of the enumerated properties.

In addition, Dr. Shklar stated: "It is insufficient to simply state, as the Block translator does, that 'Xiao-Shi' is 'niter,' and then cite a modern dictionary to 'establish' that 'niter' is potassium nitrate." With respect to both the *Grand Dictionary* and *Ben Cao,* he stated that "the translator appears to have inserted the term 'niter' into the text where the phrase 'consumer of stones' actually belongs."

Block's arguments, on the other hand, in part based on the short affidavit by Mr. Wei, substantially follow the district court's opinion. Block also challenges the competence of Hodosh's experts stating that they "either had no knowledge or training in the Chinese language or Chinese medicine or were unfamiliar with dentistry or medicine generally." Block also emphasizes that the Chinese references correctly disclose many of potassium nitrate's characteristics, like burning with a violet flame, useability for making signal fires and gun powder, and its water solubility; these three properties of xiao shi in the Chinese references definitely confirm, according to Block, that xiao shi is potassium nitrate, KNO_3.

B. *The European Prior Art*

This art is contained in six references and was not relied upon to any significant degree by Block or the district court. Hodosh scarcely mentions it on appeal, instead preferring to show the existence of genuine issues of material fact with respect to the Chinese references. After concluding that using potassium nitrate to cure tooth pain would have been obvious from Rosenthal in view of the Chinese art, the court stated: "Such holding is strengthened by the European prior art which, while ambiguous because of the several conflicting definitions in the term 'niter,' at least suggest to one skilled in the art that potassium nitrate ought to be tried as a cure for tooth pain in general."

Block submitted no affidavits that addressed the substance of the European references. Hodosh's Dr. Shklar, on the other hand, stated why this art, part of the "humors, spirits and Alchemy of the Dark Ages" having whatever medicinal effect they did by virtue of their use of wine, opium, or other narcotic substances, would have been questioned by one skilled in the art. He specifically contends that Block's translation of "nitre" is erroneous: "it is common knowledge that these terms meant sodium carbonate and/or sodium carbonate-sodium bicarbonate mixture. . . ."

To afford a glimpse of the nature of these references, an interesting and typical excerpt, one quoted by the district court, based upon a statement by the long since deceased French surgeon Guy de Chauliac reads that "a mixture of 'cuttlebone, small white sea shells, pumice, burnt stag's horn, *nitre,* alum, rock salt, burnt roots of iris, aristolochia, and reeds' could create an effective dentifrice." (District court's emphasis.) Three of the European references are based on that statement. The district court noted the others:

> Additionally, a 1693 treatise by the British Professor of Physics William Salmon states that nitrum "held in the Mouth . . . immediately helps the Toothach, if burnt and used in a Dentifrice, it cleanses and whitens the Teeth." . . . Similarly, a reference work by Hardianus a Mynsicht, translated into English in 1682, describes a mixture, including "nitre" as a "tincture for the toothache." . . . Finally, Pliny the Elder, in his *Historie of the World, The Second Tome,* translated into English in 1601, describes the use of nitre to "easeth the toothach, if the mouth and gums be washed therwith," or if burned, as a dentifrice. [Reference to Exhibits omitted.]

With this description of both the Chinese and European references, and of what they represent as a whole, in hand, we consider the proper application of the *Graham* standards and their effect upon the propriety of summary judgment in this case. *See generally Graham* v. *John Deere Co.,* 383 U.S. 1, 17 [148 USPQ 459, 467] (1966); *Panduit Corp.* v. *Dennison*

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Manufacturing Co., 774 F.2d 1082, 227 USPQ 337 (Fed. Cir. 1985).

OPINION

A. *Summary Judgment*

Summary judgment, in patent as in other cases, is appropriate where there is no genuine issue of material fact, and the movant is entitled to judgment as a matter of law. *See Molinaro* v. *Fannon/Courier Corp.* 745 F.2d 651, 653-54, 223 USPQ 706, 707 (Fed. Cir. 1984). The movant bears the burden of demonstrating the absence of all genuine issues of material fact, and the district court must view the evidence in a light most favorable to the nonmoving party and draw all reasonable inferences in its favor. *See United States* v. *Diebold, Inc.,* 369 U.S. 654, 655 (1962); *Palumbo* v. *Don-Joy Co.,* 762 F.2d 969, 973, 226 USPQ 5, 7 (Fed. Cir. 1985). The party opposing summary judgment must show an evidentiary conflict on the record; mere denials or conclusory statements are not sufficient. *Barmag Barmer Maschinenfabrik AG* v. *Murata Machinery, Ltd.,* 731

F.2d 831, 836, 221 USPQ 561, 564 (Fed. Cir. 1984). Summary judgment is authorized where it is quite clear what the truth is. *Sartor* v. *Arkansas Natural Gas Corp.*, 321 U.S. 620, 627 (1944).

B. *The Issues Below*

The decision and opinion of the district court granting summary judgment dealt with two issues: the first was whether the '006 patent is invalid as anticipated under §102(b), the court holding it is not; and the second was whether the '006 patent is invalid for obviousness under §103, the court holding that it is. Hodosh of course appeals the summary judgment with respect to only the issue on which it lost -- obviousness and Block has not appealed. Because we are remanding for trial, however, we will comment briefly on anticipation to make it clear that we deem that question to have been conclusively disposed of in this case and because it is closely related to the obviousness issue.

1. *Anticipation, §102(b)*

We agree entirely with the district court's holding that the '006 patent is not invalid as anticipated because there is no issue of fact that none of the prior art references discloses every element of the claimed invention. This issue was, therefore, appropriately and properly disposed of by summary judgment.

We do not agree, however, with some of the district court's remarks about anticipation, in particular, that the unavailability of the Chinese references and whether one skilled in the art could locate them with "reasonable diligence" bears on whether those references anticipate the claimed subject matter. Whether a reference is available as prior art and whether it anticipates (i.e., contains every claimed element) are separate questions. Moreover, the district court's determination that the references are unavailable for §102 purposes seems to be inconsistent with the approach subsequently taken by the district court in determining obviousness. The court later used these same references to support its holding that the claimed subject matter would have been obvious at the time the invention was made to one of ordinary skill in the art.

2. *Obviousness, §103*

[1] Questions of material fact remain with respect to the meaning of various terms used in the Chinese and European references and we therefore hold that summary judgment on the ground of obviousness of the claimed invention was improper.

The district court's statement that ya tong means tooth hypersensitivity as well as tooth pain is the resolution of a head-on factual controversy. The court improperly drew the inference against Hodosh, the nonmoving party, that a statement about ya tong made to the German Patent Office by Dr. Hodosh's German patent agent was made with knowledge of the Chinese references. The statement in question occurred seven years after the '006 patent issued in connection with Dr. Hodosh's counterpart German application. The statement was: "The supersensitivity of dentine has been known for a long time and can be traced back 4000 years to the Chinese where it was known as 'Ya Tong'." Hodosh in this suit disclaims this statement urging that it was factual error.

There is no evidence that the above statement was based on the Chinese references or that Dr. Hodosh conveyed this information to the German patent agent. The important fact question as to the meaning of ya tong cannot be overcome simply by styling this statement an admission binding on Hodosh. Hodosh is entitled, as Block essentially concedes, to rebut the statement with evidence to the contrary. Hodosh will have that chance at trial.

Nor does the statement in the affidavit of Block's expert, Dr. Wei, that ya tong means tooth hypersensitivity eliminate the presence of the question of the meaning of ya tong. As the Supreme Court long ago observed, "Ex

perience has shown that opposite opinions of persons professing to be experts, may be obtained to any amount. . . ." *Winans* v. *New York and Erie Railroad Co.*, 62 U.S. 88 (1859). The substance of Dr. Skhlar's affidavit on behalf of Hodosh goes far beyond merely denying that ya tong means tooth hypersensitivity and thus is more than adequate to show an evidentiary conflict on the record with respect to this crucial point, thus precluding summary judgment. *Cf. Union Carbide Corp.* v. *American Can* Co., 724 F.2d 1567, 1571, 220 USPQ 584, 587-88 (Fed. Cir. 1984).

Furthermore, a genuine issue of material fact exists with respect to the meaning of the terms nitre, nitrum, and nitri as used in the European references. Dr. Sklhar's affidavit is more than adequate to withstand the challenge of this summary judgment motion. A reasonable inference that these terms are sodium, as opposed to potassium, compounds is permissible; Hodosh has shown an evidentiary conflict on the record. The European references, Dr. Sklhar explained in his affidavit, are based on the 77 A.D. writings of Pliny The Elder, who understood these terms to mean "sodium carbonate and/or a sodium carbonate-sodium bicarbonate mixture."

The obviousness determination here, given the existence of genuine material issues of fact with respect to the meanings of terms used in these references, is not suitably disposed of by summary judgment under the rules pertaining thereto. *See generally Palumbo,* supra, and *Lemelson* v. *TRW, Inc.*, 760 F.2d 1254, 1260-61, 225 USPQ 697, 700-01 (Fed. Cir. 1985). The fact issues herein must be resolved by trial in which the conflicting views of the experts will be subject to the refining fire of cross examination, a more effective means of arriving at the legal conclusion of obviousness vel non than perusal of ex parte affidavits and declarations of partisan experts lobbed at each other from opposing trenches.

We observe, for the benefit of the trial court, that we are totally unimpressed by Block's forensic device of comparing the Rosenthal prior art toothpaste formula and the Hodosh toothpaste example in parallel columns and then asserting, as though it were filled with significant meaning, that the "only difference is the use of potassium nitrate in place of strontium chloride," or that "the Hodosh patent merely substitutes potassium nitrate for strontium chloride." This device was pushed to the limit in oral argument by pointing out that the Hodosh toothpaste has the *same* formula, *except* for the active desensitizing ingredient, down to the last decimal point. This argument is meaningless on the obviousness issue. "Sensodyne" and apparently other desensitizing toothpaste formulae being well known as commercial products, it is entirely clear that Dr. Hodosh's invention was the discovery of an apparently superior *desensitizing agent* and he never thought it was a toothpaste formula. He made that invention even if it should later be decided that it was known to the Chinese. It is apparent that Hodosh's patent solicitor merely adopted the prior art Rosenthal toothpaste base formula as a convenient example to illustrate the kind of a paste in which the Hodosh desensitizer might be used, which was within his right. The similarities -- indeed, identity -- of the paste bases is irrelevant in considering the issue of the unobviousness of the desensitizer. The Rosenthal patent, cited as prior art by Hodosh in his patent specification, was the jumping-off place for the description of his discovery. Hodosh does not claim to have been the first inventor of a desensitizing toothpaste; he claims to have improved it. The issue for trial is whether his improvement would have been obvious. [5]

C. *Secondary Considerations*

The district court refused on the motion for summary judgment to consider the evidence of secondary considerations. After acknowledging its existence and the arguments based on it, it stated:

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> However, the court continues to find that the Hodosh patent is invalid on grounds of obviousness; these secondary considerations stem not from the novelty or inventiveness engendered by substituting potassium nitrate in an already existing formula, but from a lack

of knowledge on the part of those in the field of the references here cited. That lack is here overcome by the presumption of omniscience discussed, *supra,* a rule of law by which the court is bound, whatever its merits.

[2] That secondary considerations are not considered unless there is evidence that those in the industry knew of the prior art is a non sequitur. Evidence of secondary considerations is considered independently of what any real person *knows* about the prior art. These considerations are *objective* criteria of obviousness that help illuminate the subjective determination involved in the hypothesis used to draw the legal conclusion of obviousness based upon the first three factual inquiries delineated in *Graham.* Thus, to require that actual inventors in the field have the omniscience of the hypothetical person in the art is not only contrary to case law, *see Kimberly-Clark* v. *Johnson & Johnson,* 745 F.2d 1437, 223 USPQ 603 (Fed. Cir. 1984), but eliminates a useful tool for trial judges faced with a nonobviousness determination.

The secondary consideration evidence of record and the additional evidence likely to be submitted at trial must be considered in the obviousness determination. *See generally Fromson* v. *Advance Offset Plate, Inc.,* 755 F.2d 1549, 1557, 225 USPQ 26, 32 (Fed. Cir. 1985).

Conclusion

The grant of summary judgment of invalidity is *reversed* and the case is *remanded* for trial in accordance with this opinion.

REVERSED AND REMANDED

Footnotes

Footnote 1. A certificate of reexamination confirming the patentability of claims 1-6 of the '006 patent was issued June 21, 1983, as a result of Hodosh's request for reexamination in 1982. Only one of the prior art references involved here, the Rosenthal patent, infra, was considered in the reexamination.

Footnote 2. Block also initiated regulatory proceedings designed to delay or prevent Richardson-Vicks' marketing of "Denquel." Block, having allegedly failed to comply with Food and Drug Administration (FDA) procedures before marketing "Promise" and "Sensodyne-F" in competitive response to Richardson-Vicks' introduction of "Denquel," is currently defending itself in forfeiture proceedings initiated by the FDA.

Footnote 3. The Ming Dynasty (1368-1644 AD) was marked by the restoration of traditional institutions in China and the development of the arts, especially in porcelain, textiles, and painting.

Footnote 4. Dr. Shklar is the Charles A. Brackett Professor of Oral Pathology at the Harvard School of Dental Medicine, and is an acclaimed expert in dentistry. He is also an expert on the history of dentistry and holds membership in the American Academy of the History of Dentistry.

Footnote 5. Our comments on the district court's obviousness determination generally include the following tenets of patent law that must be adhered to when applying §103: (1) the claimed invention must be considered as a whole (35 USC 103; *see, e.g., Jones* v. *Hardy,* 727 F.2d 1524, 1529, 220 USPQ 1021, 1024 (Fed. Cir. 1984) (though the difference between claimed invention and prior art may seem slight, it may also have been the key to advancement of the art)); (2) the references must be considered as a whole and suggest the desirability and thus the obviousness of making the combination *(see, e.g., Lindemann Maschinenfabrik GmbH* v. *American Hoist and Derrick Co.,* 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984); (3) the references must be viewed without the benefit of hindsight vision afforded by the claimed invention *(e.g., W.L. Gore & Associates, Inc.* v. *Garlock, Inc.,* 721 F.2d 1540, 1553, 220 USPQ 303, 313

(Fed. Cir. 1983)); (4) "ought to be tried" is not the standard with which obviousness is determined *(Jones,* supra, 727 F.2d at 1530, 220 USPQ at 1026); and (5) the presumption of validity remains constant and intact throughout litigation (35 USC 285; *e.g., American Hoist & Derrick Co. v. Sowa & Sons, Inc.,* 725 F.2d 1350, 1359-60, 220 USPQ 763, 770 (Fed. Cir. 1984)).

- End of Case -

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